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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,909	JACKOWSKI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2006*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 39-46* is/are pending in the application.

4a) Of the above claim(s) *39-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 24, 2006 has been entered.

2. Claims 1 and 39-46 are pending in the instant application.

Claims 39-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made by original presentation in Paper mailed on May 28, 2004.

Claim 1 is under examination in the instant office action.

3. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments filed on January 24, 2006 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 101

6. Claims 1 stands rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility essentially for reasons of record in section 6 of Paper mailed on August 30, 2005.

Claim 1, as currently presented, is directed to a biopolymer marker consisting of amino acid sequence 2-14 of SEQ ID NO: 1 which evidences a link to Alzheimer's disease (AD). The instant specification provides a disclosure of a protocol, under which samples of blood collected from AD patients, age-matched controls and pooled control samples were analyzed by using mass spectrometric and chromatographic techniques. The results of the analysis are presented in Figures 1-6 and also within the text of the instant specification. Specifically, finding of the "disease specific marker" identified by an amino acid sequence is presented at page 46 of the instant specification. At bottom of page 46 continuing to page 47, Figures 1, 3 and 5 are described as "photographs of a gel which is indicative of the presence/absence of the marker in disease vs. control and, in cases where the marker is always present, the relative strength, e.g. the up or down regulation of the marker relative to categorization of diseases state is deduced". Brief description of the figures (page 37) does not contain any disclosure of how fragment 2-14 of SEQ ID NO: 1 corresponds to the bands as shown in Figures 1 and 4. The Examiner maintains that based on the information presented in the instant specification as originally filed, the instant claimed invention, an isolated biopolymer marker 2-14 of SEQ ID NO: 1, asserted to be useful for diagnostics and therapeutics of Alzheimer's disease, clearly lacks specific and substantial credible real-world utility and, therefore, the instant invention does not meet the requirements of 35 U.S.C. 101.

Applicant traverses the instant rejection on the premises that:

1) the Examiner's statements are contradictory and reveal an incomplete understanding of the invention (pages 7-9 of the Response);

2) the instant specification presents a clear and unambiguous definition of "biopolymer marker" (pages 10-13);

3) the specific and substantial credible utility of the claimed biopolymer marker for diagnostics and/or therapeutics of Alzheimer's disease (AD) is based on the showing of "differential expression" of the marker 2-14 of SEQ ID NO: 1 between samples obtained from AD patients and age matched normal control (pages 9-10 and 14-18);

Applicant's arguments have been fully considered but are not persuasive for the following reasons.

1) Applicant submits that acknowledgement that complement C3 precursor protein is known in prior art to be associated with Alzheimer's disease together with the statement that a fragment of that protein (protein 2-14 of SEQ ID NO: 1) is not useful for diagnosis or treatment of Alzheimer's disease demonstrates that the Examiner's statements are contradictory (page 7 of the Response). The Examiner disagrees. The prior art recognizes that complement C3 precursor protein is associated with Alzheimer's disease pathology; however, its specific role in AD is currently not known. Moreover, there is no information available in prior art to suggest that complement C3 precursor protein or its fragments could be useful as markers for AD. Because the instant specification fails to present any factual evidence that the instant fragment 2-14 of SEQ ID NO: 1 could be used as a marker for AD (see explanations in the previous office actions of record and reasons in the instant office action), the Examiner maintains that the fact that the

instant protein of SEQ ID NO: 1 is a fragment of a known polypeptide, complement C3 precursor protein, potentially associated with AD, does not allow a conclusion that it is useful as a marker for AD. The art discloses many proteins potentially associated with Alzheimer's disease; however, this alone does not allow a conclusion that fragments of these proteins are useful as diagnostic markers.

The Declaration of Lander under 37 CFR 1.132 filed on January 24, 2006 has been fully considered. The Declaration is insufficient to overcome the rejection of claim 1 based upon lack of utility and enablement as set forth in the last Office action because: the Declaration presents a copy of Figure "DEAE 3 (Elution) AD vs. Age Matched AD (Control)", in which "decreased expression of the claimed peptide in Alzheimer's disease is also clearly shown". However, the Examiner does not doubt or dispute the results of differential expression of the instant claimed protein 2-14 of SEQ ID NO: 1. The main point of disagreement appears to be the interpretation of these results and what constitutes a specific and substantial credible utility. The Examiner maintains that practical utility of the instant claimed protein 2-14 of SEQ ID NO: 1 cannot be simply extrapolated from the data limited to its differential expression. A significant further research is required to identify or reasonably confirm a "real world" context of use of the claimed protein, see *Brenner v. Manson.*

2) The instant specification presents several definitions of a "biopolymer marker" (see pages 5, 6 especially 11 and 21), essentially that it is a polymer of biological origin (bottom at page 21), which can be present/absent/down-regulated/upregulated with respect to a disease condition (page11). However, according to Webster dictionary "a marker" is "one that marks or distinguishes". The instant invention is based on finding that a peptide fragment 2-14 of SEQ ID

NO: 1 is differentially expressed in patients suspected of having AD from control normal individuals. There appears to be no further information presented in the instant specification as to what constitutes finding of a peptide 2-14 of SEQ ID NO: 1 in a sample. For example, if a peptide 2-14 of SEQ ID NO: 1 was found in a sample obtained from a patient, what would that mean to the skilled practitioner? Does it mean that a patient has AD, or is at risk of developing the disease? The instant specification fails to provide any factual evidence that finding of a peptide 2-14 of SEQ ID NO: 1 could lead to any meaningful determination for diagnosis of Alzheimer's disease or would be useful for treatment of Alzheimer's diseases, as asserted by Applicant. Thus, in order to practice the claimed invention, a skilled artisan would have to engage in a substantial amount of further research to establish the utility of the claimed peptide 2-14 of SEQ ID NO: 1 in the diagnostics of Alzheimer's.

At page 13 of the Response, Applicant argues that "one of ordinary skill in the art would not doubt the veracity of Applicants asserted use for the claimed peptide [...] since situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a diseases state versus expression in a normal physiological state" and refers to the publication of Andreasen et al. submitted with the Response. The Examiner fully agrees that in cases when a disclosure contains specific information of what critical levels or forms of the claimed molecular marker are diagnostic of the disease state, such as, for example, in publication of Andreasen et al. (Arch. Neurol. 1999, 56, pp.673-80) where "Mean +/- SD levels of CSF-beta-amyloid (1-42) were decreased (P<.001) in patients with AD (709+/-304 pg/ml) compared with controls (1678 +/- 436 pg/ml)", "CSF-beta-amyloid" would be considered as a proper biomarker of AD. However, this

is not the fact pattern here. In the instant case, the specification discloses the finding of differential expression of protein 2-14 of SEQ ID NO: 1 in samples of patients with AD *vs.* normal patients and presents an assertion that this protein 2-14 of SEQ ID NO: 1 is useful as a marker for Alzheimer's disease. It is obvious that a skilled practitioner would have to engage in a significant further research to establish what amount of the instant claimed protein is diagnostic of Alzheimer's disease.

3) With respect to "differential expression" of the peptide 2-14 of SEQ ID NO: 1, it is important to point out that the Examiner never disputed that the instant peptide 2-14 of SEQ ID NO: 1 is differentially expressed in the samples of patients suspected of having Alzheimer's disease. However, differential expression as indicated in Figure 1 is a relative term based on the levels found in the samples analyzed. One skilled in the art readily understands that in order to use the peptide 2-14 of SEQ ID NO: 1 as a biomarker for Alzheimer's disease, a point of reference that is critical for diagnosis with respect to the level of differential expression of the claimed peptide must be disclosed. In the absence of this critical information, it is unclear as to how one of skill in the art can reasonably determine if the peptide fragment 2-14 of SEQ ID NO: 1 can be used as a diagnostic marker for Alzheimer's disease. Thus, a skilled practitioner would have to resort to a substantial amount of further experimentation in order to be able to practice Applicant's invention. It is a matter of law that the claimed invention must be useful in currently available form, which precludes any further experimentation to establish the utility of the claimed invention.

At page 14 of the Response, Applicant submits that because the instant specification shows differential expression of protein 2-14 of SEQ ID NO: 1 between AD patients and normal

healthy control, "one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition". The Examiner strongly disagrees that "differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease" (middle at page 14 of the Response). One skilled in the art readily appreciates that many proteins are differentially expressed between healthy and "diseased" tissues (cancer cells, for example, overexpress a plurality of proteins by virtue of uncontrolled proliferation); however, not all of these proteins constitute biomarkers, as molecules that allow to distinguish disease *vs.* healthy state.

On pages 15-19 of the Response, Applicant argues that discovery of a peptide marker constitutes a small discovery within the progress of science leading to larger discoveries of treatment of Alzheimer's disease and refers to publication of Patel. The Examiner fully agrees that identification and selection of reliable biomarkers to diagnose pathological conditions is a known practice. Moreover, identification of a marker that is specifically associated with a particular condition (present/absent or present at specific altered levels as compared to normal control) constitutes a specific and substantial credible utility even if a biological role of the molecule itself is not known or disclosed. However, this is not a factual situation here. In the instant case, Applicant's invention is predicated on the finding that samples of blood taken from patients suspected of having AD contain proteins in the forms and amounts that are different form normal control samples. Applicant further extrapolates this result into a diagnostic tool for AD. Accordingly, it would appear that Applicant provides a single finding (the finding), and then presents an invitation to experiment to determine the level of differential expression of peptide 2-14 of SEQ ID NO: 1 that is diagnostic of AD, and then to assay if the peptide could be used to

diagnose AD, such as to distinguish AD from normal state and from other similar neurodegenerative conditions, as well as to treat AD.

Further, regarding the merit of the argument, there appears to be no evidence presented in Applicant's cited articles that would support a conclusion that any protein that is found to be differentially expressed under a pathological condition, could be immediately used as a marker for that condition. It is obvious to expect that many proteins are differentially expressed during Alzheimer's disease; however, not all of them can serve as diagnostic biomarkers. One skilled in the art readily appreciates that detection of differentially expressed proteins represents only the first step in identification of molecules that have a diagnostic potential. The search for a diagnostic marker is usually divided into two steps; the first step being an exploratory search to identify a subset of proteins that may be involved in physiological/pathological process and the second step, which involves a very focused research to confirm that the detected differentially expressed protein could be used as a marker. The instant specification identified a peptide that is differentially expressed between Alzheimer's samples and normal control. However, there appears no further characterization presented that would lead to the "real world" specific utility of this peptide as biomarker for AD. There is little doubt that, after complete characterization, this peptide fragment 2-14 of SEQ ID NO: 1 may be found to have a specific and substantial credible utility as a biomarker. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA. *See In re Fisher,* 2005 WL 2139421 (Sept. 7, 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as

rejecting a "de minimis view of utility" 2005 WL 2139421, at *4. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at *5. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Id.*

Just as in *Fisher* case where the Board reasoned that use of the claimed ESTs for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage," (*Id.*, slip op. at 15), in the instant case, detection of peptide 2-14 of SEQ ID NO: 1 in a sample of a patient suspected of having AD provides no meaningful information as to the diagnosis determination. While an assay that detects the presence of a marker that has a stated correlation to a specific disease condition would be considered a "substantial utility" in the context of providing a diagnostic tool, in the instant case the claimed peptide is suitable only for further research, which constitutes a utility that is not considered a "substantial utility". See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility.

Finally, with respect to limitation present in claim 1, "evidences a link to Alzheimer's disease", the Examiner maintains that disclosure of a peptide fragment 2-18 of SEQ ID NO: 1 as being linked to a pathological condition constitutes a utility, which requires further research to

identify or reasonably confirm a "real world" context of use. At present, it appears that the only information obtained from identifying the presence of a biopolymer marker 2-14 of SEQ ID NO: 1 is the determination of "a link to AD". One skilled in the art readily appreciates that many factors have a link to or are associated with a particular pathological condition. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), the court specifically stated that "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion". To grant Applicant a patent encompassing isolated fragments of a naturally occurring human protein, which are not readily usable in their current form, would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *Brenner v. Manson, Ibid*). To grant Applicant a patent on the claimed peptides based solely upon an assertion that the protein is linked to Alzheimer's disease is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted.

Thus, since the instant specification does not disclose a credible "real world" use for the isolated biopolymer markers 2-14 of SEQ ID NO: 1 in currently available form, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

7. Claim 1 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

8. No claim is allowed.

9. This application contains claims 39-46 drawn to an invention nonelected with traverse in Paper filed on March 09, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

10. This is a continuation of applicant's earlier Application No. 09/994,909. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however,

event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on 8:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.
Primary Examiner
Art Unit 1649

February 22, 2006